Remarks

Claim 9 is amended herein. Claim 15 is canceled herein. New claims 22-43 are added herein. Support for the amendment of claim 9, and new claim 22, can be found in the specification on page 9, lines 32-36, page 11, line 32 to page 12, line 15, and page 14, lines 1-4. Support for new claims 23-28 can be found throughout the specification, specifically on page 5, line 17 to page 9, line 36, such as on page 9, line 33. Support for new claims 28-43 can be found in the specification on page 12, lines 30 to page 13, line 30, and on page 5, line 17 to page 9, line 36.

The specification is amended herein to rectify a translation error.

Applicants believe no new matter is added. Reconsideration of the subject application is respectfully requested.

Telephone conference

Applicants thank Examiner Whiteman for the helpful telephone conference of July 6, 2004, wherein the support for the amendment of claim 1 and the support for claim 22 was discussed.

Election/Restrictions

Claim 11 is objected to for being drawn to non-elected subject matter. Applicants note that an election of species (with traverse) was made on June 25, 2002. This response specifically pointed to errors in the requirement for the election of species. In addition, the Office action dated October 3, 2002, stated that the species not elected from clams 3, 11, and 18 were withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to a non-elected species.

The present Office action requests cancellation of the subject matter "or other appropriate action." Applicants note that upon allowance of a generic claim, they are entitled to consideration of claims to additional species that are written in dependent form. MPEP 809.02 states that when a generic claim is rejected, claims readable on the non-elected species should be considered to be withdrawn. When the generic claim is subsequently found to be allowable, the claims drawn to the non-elected species are no longer considered to be withdrawn (see MPEP 809.02(B)(1)). As such, Applicants respectfully submit that cancellation or amendment of claim 11 is not required at this time. Applicants reserve the right to petition the requirement for an election of species.

Rejections Over the Prior Art

Claims 9, 11, 12 and 14-16 were rejected under 35 U.S.C. § 102(e) as anticipated by, or in the alternative obvious under 35 U.S.C. § 103(a), over U.S. Patent No. 6,248,722 (hereinafter the '722 patent), in view of the Gene Therapy of Osaka University. Applicants respectfully disagree with these rejections.

The '722 patent discloses the treatment of arterial disorders, such as the treatment of disorders caused by abnormal proliferation of vascular smooth muscle. The '722 patent does not disclose the treatment of subjects with ischemia related to diabetes. Thus, claims 9, 11, 12 and 14-16 are not anticipated by the '722 patent.

As discussed with Examiner Whiteman, the '722 patent discloses that "the content of HGF in the medicament may be appropriately varied depending upon diseases to be treated, target organs, patients' ages or body weights, etc. However, it is appropriate to administer in a dose of 0.001 mg to 10 mg when calculated as the HGF gene. The dose can be divided into several days or a few months."

Thus, the '722 patent teaches administration of a *single dose* of HGF gene, at 0.001 mg to 10 mg (1 μg to 10,000 μg). This single dose can be administered continuously over a single period of time, which varies from a few days to a few months.

The '722 patent does not teach, nor render obvious, intermittent repeated doses of HGF, such that a specified amount is administered to a subject every few days or every few weeks. Indeed, the '722 patent does not suggest, nor render obvious, administration of a nucleic acid encoding HGF once every few days, once every few weeks, or every three to five weeks.

Thus, Applicants submit that the '722 application does not anticipate, nor render obvious, claims 9, 11, 12 or 14-16 as amended (or any of the newly added claims).

As noted above, the '722 patent suggests treatment of arterial disorders using HGF, but does not suggest treatment of diabetic ischemia, nor does it suggest repeated administration of HGF. The Gene Therapy of Osaka University article describes a request for approval for a clinical trial by the Institutional Review Board (IRB) at Osaka University in Japan. This request was made by Dr. Morishita and Dr. Ogihara. With regard to an obviousness rejection based on the '722 patent combined with a report of a suggested study only might make it "obvious to try" HGF for the treatment of diabetic ischemia, which is not the proper standard in an obvious analysis.

In addition, neither the '722 patent, nor the Gene Therapy of Osaka University article suggests, nor renders obvious, the administration of multiple doses of a nucleic acid encoding HGF, let alone administration every few days or every few weeks. Thus, Applicants submit that the '722 patent, in combination with the Gene Therapy of Osaka University article does not

render obvious claims 9, 11, 12 or 14-16 as amended (nor would it render obvious any of the newly added claims).

In addition, Applicants note that comparative data documenting the unexpected superior result of HGF administration in the treatment of diabetic ischemia is presented in the specification on page 12, lines 17-28, and in Fig. 4. Specifically, HGF gene therapy was administered to rats with diabetic lower limb ischemia and with control (non-diabetic) lower limb ischemia. Five weeks after administration, the blood vessels were counted per unit area. The blood vessel count in rats with diabetic lower limb ischemia was significantly greater than the blood vessel count in control rats with non-diabetic lower limb ischemia. This evidence of an unexpectedly superior result in the treatment of diabetic ischemia rebuts any *prima facie* case of obviousness asserted against claims 9, 11, 12 and 14-16 (and as might be applied to the new claims added herein). Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 9, 11, 12, 15 and 16 were rejected as allegedly being anticipated under 35 U.S.C. § 102(e), or in the alternative, obvious under 35 U.S.C. § 103(a), over U.S. Patent No. 6,121,246 (hereinafter the '246 patent), or as obvious over the '246 patent in view of Gene Therapy of Osaka. Applicants respectfully disagree with these rejections.

The '246 patent teaches treatment of ischemic tissue, such as cerbrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, or ischemic cardiomyopathy by administering a nucleic acid encoding an angiogenic protein. Acute ischemia of the kidney, lung, limb or heart is a result of decreased arterial perfusion, usually from embolus or thrombosis. This condition is substantially different from chronic critical limb ischemia, wherein narrowed vessels that cannot supply sufficient blood flow to exercising leg muscles cause

claudication. As vessel narrowing increases, critical limb ischemia can develop when the blood flow does not meet the metabolic demands of tissue. Methods for treating an acute event such as embolus or thrombosis are very different from methods for treating chronic blood vessel narrowing. Thus, the '246 patent does not anticipate, or render obvious claims 9, 11, 12, 15 or 16, which are directed to the treatment of diabetic ischemic disease.

The '246 patent discloses the administration of a nucleic acid encoding an angiogenic protein into multiple sites throughout the ischemic tissue. However, the '246 patent does not disclose repeated administrations (over a few days or over a few weeks) of a nucleic acid encoding hepatocyte growth factor. As such, Applicants submit that the '246 patent does not anticipate claims 9, 11, 12, 15 or 16 as amended. Reconsideration and withdrawal of the rejection is respectfully requested.

As discussed above, the '246 patent discloses the treatment of acute ischemia, which is very different from chronic ischemic disease. The Gene Therapy of Osaka University article describes a request (by Dr. Morishita and Ogihara, the inventors of the present application) for approval for a clinical trial by the Institutional Review Board (IRB) at Osaka University in Japan. A rejection based on this suggested study only might make it "obvious to try" HGF for the treatment of diabetic ischemia, which is not the proper standard in an obvious analysis. Moreover, the Gene Therapy of Osaka University does not disclose, nor render obvious, dosing regimens wherein a nucleic acid encoding HFG is administered every few days or every few weeks.

Moreover, as noted above, comparative data documenting the unexpected superior result of HGF administration in the treatment of diabetic ischemia is presented in the specification on page 12, lines 17-28, and in Fig. 4. Specifically, HGF gene therapy was administered to rats

with diabetic lower limb ischemia and with control (non-diabetic) lower limb ischemia. Five weeks after administration, the blood vessels were counted per unit area. The blood vessel count in rats with diabetic lower limb ischemia was significantly greater than the blood vessel count in control rats with lower limb ischemia. This evidence of an unexpectedly superior result in the treatment of an ischemia in a diabetic limb rebuts any *prima facie* case of obviousness asserted against claims 9, 11, 12, 15 or 16 (and as might be applied to the new claims added herein). Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 9 and 14 were rejected as allegedly being obvious under 35 U.S.C. § 103(a) over the '246 patent, in view of the Gene Therapy of Osaka University article, and further in view of Afione et al. (*Clin Pharm.* 28:181-189, 1995). Applicants respectfully disagree with this rejection.

The '246 patent and the Gene Therapy of Osaka University article are discussed above. Afione et al. discloses the HVJ-lipsome technology. As discussed above, the Gene Therapy of Osaka University article describes a request for approval for a clinical trial. This report only might make it "obvious to try" HGF for the treatment of diabetic ischemia, which is not the proper standard in an obvious analysis. Moreover, the Gene Therapy of Osaka University article does not disclose, nor render obvious, dosing regimens using more than one administration of HGF, wherein a nucleic acid encoding HFG is administered every few days or every few weeks.

Afione et al. describes the use of HVJ liposomes to deliver a nucleic acid to a cell. Afione et al. do not make up for the deficiencies of the '246 patent or the Gene Therapy of Osaka University article, as Afione et al. does not suggest dosing regimens for nucleic acids encoding HGF, let alone repeated administrations every few days or every few weeks. As such,

Applicants submit that the '246 patent, in combination with the Gene Therapy of Osaka University and Afione et al. do not render claims 9 and 14 obvious.

Moreover, as discussed above, the data presented in the specification documenting the unexpectedly superior results obtained using nucleic acids encoding HFG in the treatment of diabetic ischemia rebut any *prima facie* case of obviousness. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

Applicants submit that the pending claims are in condition for allowance, which action is requested. If any matters remain to be discussed before a Notice of Allowance is issued, Examiner Whiteman is respectfully requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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